THE FUNCTIONS OF THE PITUITARY BODY.[1]

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Information in regard to the physiological properties of one of the glandular bodies whose secretion supposedly enters directly into the bloodstream may be gathered in numerous ways: (1) We may observe the immediate consequences of injecting its variously prepared extracts, or we may more accurately attempt to simulate the action of the hyperfunctionating gland by repeated injections, by feeding, or by implantations. (2) We may, on the other hand, study the reverse conditions comparable to lowered glandular activity by observing the effects of total or partial destruction or extirpation. (3) We may approach the subject in a roundabout way by observing the alterations in its histological appearance and activity which follow the removal or injury of one or another of the allied or interrelated glandular structures. (4) We may gain some further insight into its function by the changes which occur not only in conditions of disease, but also during certain unusual physiological states, such as pregnancy, hibernation, puberty, and the menopause.

Let us consider *seriatim*, certain of the facts which these several methods have disclosed in regard to the functions of the hypophysis—facts which are merely steps toward the ultimate goal of determining the chemical nature of the active principle or principles to which it owes its activities.

1. Simulated Oversecretion by Injections, Feeding, etc. Through the interest aroused in the possible importance of the pituitary body as an active organ which followed Marie's early papers, studies by injection methods were made at various hands. As is well known, it was shown by Oliver and Schäfer that the glandular extract, even when raised to the boiling point, led to a rise in blood pressure, and later by Howell that this substance was confined to the posterior lobe of the gland—the pars nervosa and its epithelial investment. The pressor response following this primary injection was found to be more enduring than that produced by adrenalin and to be accompanied by a definite slowing of the pulse, which occurs even when the vagi are cut or atropine is used. Even on the first injection, however, there may be an initial depressor reaction, and this, on subsequent injections, may be the only response. It was subsequently brought out by Schäfer and Magnus that this active principle of the posterior lobe distends

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[1] Read at the combined session of the American Physiological Society and Section K of the American Association for the Advancement of Science, Boston, December 28, 1909.

the kidneys and increases the flow of urine. It shows a further resemblance to adrenalin in dilating the pupil; and similar atheromatous changes in the arteries are said to follow the long-continued administration of either extract.

These responses to extracts of glands of lower animals have recently been shown by Halliburton, Candler, and Sikes[2] to hold true for extracts of the human gland, and, using Baumann's method for the detection of iodine, they have made the important observation that the hypophysis, though capable of secreting colloid, differs form the thyroid gland in being iodine free.

All similar physiological reactions have proved negative so far as the injection of anterior lobe extract is concerned. We have occasionally observed a slight pressor effect in partially thyroidectomized animals, but we have found that the most striking consequence of anterior lobe injection occurs as a thermic response in animals suffering from hypopituitarism, a rise of 2° to 4° C. in body temperature being not unusual.

With Dr. S. J. Crowe, the attempt has been made to study the effects upon nutrition of repeated injections, and it is our experience, in partial agreement with others, that the extract of the entire gland, or of the posterior lobe alone, administered daily over long periods of time, leads to progressive emaciation, often with marked degenerative changes in the spleen and central necroses in the liver. Similar evidences of autointoxication, it may be added, we have not uncommonly seen after operative removal of the gland.

No conclusive results were obtained by repeated daily hypodermic administration of anterior lobe extract in the several puppies subjected to this treatment. They rather tended to lose weight than otherwise, and this has been the experience of Caselli and others. Possibly in these investigations too large an amount of extract has been introduced, or some pars intermedia may have been included in the preparation. Likewise anterior lobe injections in animals in the cachexia hypophyseopriva stage failed in any striking way to postpone the outcome of a total hypophysectomy, though we have been somewhat more successful in tiding over this critical condition by heterotransplants placed in the cerebral subcortex.[3]

The necessity of clearly distinguishing between the properties of anterior and posterior lobes becomes very apparent in all of these observations. And this is no less true for the proper interpretation of the results of feeding experiments. Ingestion of the entire pituitary, as was shown by the experiments of Thompson and Johnston,[4] leads to a loss of weight by stimulating metabolism;

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[2] Quarterly Journal of Experimental Physiology, 1909, ii, 229.

[3] Crowe, Cushing, and Homans, Quarterly Journal of Experimental Physiology, 1909, ii, 389.

[4] Journal of Physiology, 1905, xxxiii, 189.

an effect which in all probability can be attributed to the inclusion of the posterior lobe extract in the preparation which they employed.

Sandri[5] observed no effect upon the growth of young mice from a two months' feeding of the pars anterior of beef pituitary, whereas those similarly fed on posterior lobe substance showed a notable arrest of development. Positive results, however, have recently been obtained by Schäfer,[6] who found that the growth measurements in a series of white rats fed upon powdered anterior lobe showed a definite increase over the controls; and certain observations, at present being conducted by Dr. Emil Goetsch in the Hunterian Laboratory, tend to give support to Schäfer's observations, at least so far as the effects of anterior lobe feeding on the body weight and growth of partially hypophysectomized puppies is concerned.

As is true of other ductless glands, the effort to increase secretion by the ingrafting of heterotransplants, whether in spleen, bone-marrow, or elsewhere, has been disappointing, for, on the principle elucidated by W. S. Halsted, it appears that transplants "take" only when there is some physiological glandular deficiency; hence it is impossible to study the consequences of hypersecretion in this way.

Injection and feeding experiments therefore show: (1) That in the posterior lobe or its epithelial investment is a substance which raises blood pressure, dilates the pupil, causes diuresis, and, when given subcutaneously or injected over long periods of time, is likely to produce marked nutritional disturbances; and (2) that ingestion of the anterior lobe, at least in the case of young animals, appears to have some influence in stimulating growth, and that injection of its extract in states of hypopituitarism leads to a temporary pyrexia.

2. SIMULATED UNDERSECRETION BY TOTAL OR PARTIAL DESTRUCTION OR REMOVAL OF THE GLAND. Attempts at surgical removal have been made by various operative methods on various animal species and with seemingly variable results—to be explained doubtless by incomplete extirpation and the failure to control the surgical procedure by a careful examination of the infundibular region in serial sections in order to exclude the possibility that viable fragments have been left behind. Sir Victor Horsley's original statement, based on the supposedly total hypophysectomy in two dogs, that no disturbance follows the loss of the gland, has been given wide credence, and subsequent observations by Marienesco, Vassale, Fichera, Gley, and many others have not been sufficiently conclusive to modify this generally accepted view.

Paulesco, of Bucarest, however, in 1908, using an improved surgical approach to the base of the brain, succeeded in removing the gland in its entirety from 22 dogs and 12 cats, and found that its loss leads to a peculiar train of symptoms invariably followed by death in the course of two or three days.[7] In all of the animals which survived, viable fragments of the anterior lobe were invariably found postmortem at the base of the brain. He furthermore was led to believe that the mere separation of the stalk was comparable to a total hypophysectomy.

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[5] Riv. di Path. Nerv. e Mentale, 1908, xiii, 518.

[6] Croonian Lecture, Proceedings of the Royal Society, 1909, lxxxi, 442.

Since the publication of these observations in 1908 an article by Gemelli,[8] of Milan, has appeared, criticizing Paulesco's operative method and recording a series of operations on cats by an intrabuccal approach, with contrary results. Following Gemelli's procedure a number of these animals were operated upon a year ago in the Hunterian Laboratory by Dr. John Homans, and symptoms, in every way comparable to those observed in the canine, followed all complete extirpations.

It can be appreciated that observations of this kind, requiring not only an elaborate and delicate operation, but a thorough histological postmortem examination, not only of the other ductless glands, but of the infundibular region by serial sections, are not a light undertaking, and the histological corroboration of the operative results were neglected in the fifteen experiments carried out with Dr. L. L. Reford in 1908.[9] During the past year, in collaboration with Drs. S. J. Crowe and John Homans, a series of a hundred hypophysectomies was made the object of a more thorough investigation, the detailed report of which is forthcoming. These observations lend further support to Paulesco's main contention as regards the consequences of a total hypophysectomy, but they have brought out the fact that not only is the operation much more easily conducted in young than in adult animals, but also that the acute symptoms of cachexia hypophysepriva do not set in in puppies until a period varying from ten days to three weeks after the operation. They have shown also that a stalk separation need not be fatal, for the epithelial lobe need not lose its vitality and the gland may become reattached in a nearly normal physiological relation to the infundibulum. Loss of the posterior lobe, furthermore, leads to no obvious disturbances in the animal's condition, whereas removal of the anterior or epithelial lobe—the posterior lobe remaining *in situ*—is equivalent to a total hypophysectomy.

The symptoms of cachexia hypophyseopriva are unmistakable, and, as has been indicated, set in after a variable period of from thirty-six hours to two weeks or so after the operation, depending upon the age of the animal. With the exception possibly of a transient glycosuria, with or without polyuria, the animal in the interval appears perfectly normal in all respects. The onset of the symptoms is characterized by inactivity with a little stiffness and unsteadiness of gait and lowering of body temperature; an awkward arching of the back with incurvation of the tail is characteristic. In the course of a few hours or days, depending on the rapidity of progress in different ages, there is a further fall in temperature, together with slowing of pulse and respiration; and irregular muscular contractions occur, often with snapping of the jaw—coarse shivering movements which are not entirely unlike the tremors characterizing tetany. The animal becomes more and more lethargic and indifferent to his surroundings and finally lapses into an anesthetic state of coma, with slow pulse and an occasional deep diaphragmatic respiratory movement; and it is often difficult to tell just when life ends. Before this occurs the fall in temperature may have been extreme—to 20° C. or lower, almost room temperature.

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[7] N. C. Paulesco, L'hypophyse du cerveau, Vigot Frères, Paris, 1908.

[8] Folia Neurobiologica, 1908, ii, 167.

[9] Reford and Cushing, Is the Pituitary Gland Essential to the Maintenance of Life? Johns Hopkins Hospital Bulletin, 1909, xx, 105.

In a series of hypophysectomized animals which have been observed this fall, Dr. Goetsch called attention to the fact that the heart is often found beating, or may resume its activity, when exposed post-mortem, and, like the batrachian organ, may continue to pulsate sometimes for half an hour after its removal from the body if placed in salt solution.

An examination of the other ductless glands from this series of animals has shown definite histological alterations, which are now under investigation. Some of the most striking changes have been observed in the thyroid and testis.

Our chief interest, however, has been centred in the animals who have survived the operation for long periods and in whom a postmortem examination has invariably shown that viable fragments of the anterior lobe have been left *in situ*, whether accidentally or, as in our later series, purposefully. These partial operations may be divided into three categories: (1) Those with removal of the posterior lobe alone; (2) those with a partial loss of the anterior in addition to the posterior lobe; and (3) those with total or fractional extirpation of the anterior lobe alone.

Owing to the persistence of a well-developed cleft, the posterior lobe in the canine is readily dislocated from the rest of the gland and can be removed as an intact fragment. As I have already stated, such a partial operation leads to no apparent disturbance in the animal's condition, though it must be admitted that fragments of pars intermedia which remain viable and possibly show hypertrophy are necessarily left adherent about the infundibular stalk in even the most complete operations. In these cases we have observed no striking post-operative alteration in blood pressure or urinary secretion, such as might be expected in view of the known effects of extracts from this part of the gland. On the other hand, in those animals which have suffered a partial loss of the anterior lobe and have subsequently been observed for a long period of time, definite nutritional disturbances have frequently occurred. Thus, in puppies a partial hypophysectomy leads to a persistence of infantilism, and though the animals are fairly lively and playful, they remain undersized, acquire no secondary sexual characteristics, show a tendency to hypotricosis, often have a subnormal temperature, and are otherwise comparable to some of the clinical conditions to be described. Feeding experiments are being undertaken in some animals of this series.

In the adult animals subjected to a partial hypophysectomy other changes have been noted which suggest a reversion to the infantile type. A number of them have in the course of a few months become exceedingly fat, suggesting the experimental reproduction of the well-recognized clinical condition which accompanies certain cases of tumor of the hypophysis unassociated with akromegaly. In several adult males, furthermore, there has been a very evident atrophy of the external genitals, the tubules of the testis showing a tendency to reversion to the infantile type with loss of spermatozoa, absence of mitosis and other peculiar changes in the spermatogenetic epithelium, as well as certain alterations in the interstitial cells of Leydig.

Histological changes are also apparent in the thyroid and islands of Langerhans, and possibly also in thymus, adrenals, and ovaries, but we cannot speak definitely of these changes at the present time.

The view is a natural one that the glycosuria, for example, seen so often not only in the clinical cases of hypophyseal disease,[10] but also in these experimental conditions, may possibly be secondary to some alteration in the pancreatic islets rather than due to the primary hypophyseal lesion; and similarly that the adiposity may be consequent upon a testicular or ovarian disturbance comparable to the adiposity which follows castration or spaying.

3. Hypophyseal Changes Secondary to Lesions of Other Ductless Glands. Of these changes I cannot speak from personal experience, though alterations in the gland secondary to castration and to thyroidectomy have been described by various writers. Thus, the gland has been found to be uniformly larger, by measurement and weight, in castrated horses than in studs, and the same is true of cattle.[11] Gley demonstrated in rabbits that the gland enlarges after experimental thyroidectomy; Stieda and Rogowitsch

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[10] Borchardt estimates (Zeitschrift f. klinische Medizin, 1908, lxvi, 332) that 35 per cent. of the reported cases of akromegaly have shown glycosuria, and on the view that the glycosuria might be due to hyperactivity of the gland he injected large doses of pituitary extract into dogs and rabbits, and in the latter glycosuria constantly occurred. This he interpreted as evidence that akromegaly is due to hyperfunction. We find that a temporary glycosuria, however, is a very frequent sequel of total or partial extirpations, so that a disturbance of carbohydrate metabolism may seemingly accompany either hyper- or hypopituitarism.

[11] Schütz, Wiener med. Wochenschr., March 29, 1909, 606.

described the change as an hypertrophy of the anterior lobe, and Cimoroni has shown that it is due to the loss of thyroid rather than parathyroid tissue. Herring,[12] however, finds the chief alteration in the pars nervosa, pars intermedia, and ependymal cells of the third ventricle.

That the reverse is true, namely, alterations in other glands secondary to hypophyseal lesions, we have abundant evidence, and it is just as natural that a lesion primarily involving some other of the family of ductless glands should bring about some functional readjustment which is productive of definite gross and histological changes in the hypophysis. The close physiological interrelation of all of these bodies, as emphasized by Falta, is most probable, and many illustrations may be drawn from conditions of experiment, as well as of disease. In the case of the hypophysis, however, just what the recognizable alterations signify awaits an interpretation which can only be forthcoming when we gain a more thorough knowledge of the exact physiological properties, particularly of the various cells which comprise the epithelial portion of this gland.

4. ALTERATIONS IN THE GLAND IN DISEASE AND IN VARIOUS STATES OF FUNCTIONAL ACTIVITY. Since Marie called attention to the association of akromegaly with hypophyseal tumors a number of phenomena in addition to the apparant relation of the gland to body growth have come to be recognized as frequent accompaniments of hypophyseal lesions.[13] Among these may be mentioned glycosuria, polyuria, impotence or amenorrhœa in adults, and the delayed or nonappearance of secondary sexual characteristics in the young; both of the latter conditions being oftentimes accompanied by a peculiar and occasionally an excessive degree of adiposity. Other less striking manifestations may occur, such as a subnormal temperature, hebetude, slowing of the pulse and falling out of the hair, with other cutaneous changes—all of them symptoms which, as we have seen, may appear in one or another of the experimental conditions already described.

The actual association of an hypophyseal lesion with akromegaly is by no means generally conceded, despite the obvious tumor or enlargement so frequently observed, for a number of autopsies of undoubted cases of akromegaly have shown a pituitary body which has been regarded as practically normal. Further confusion has arisen owing to the description of a group of cases by Fröhlich and others in which tumors in the infundibular neighborhood were accompanied by adiposity and infantilism in the absence of akromegaly.

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[12] Quarterly Journal of Experimental Physiology, 1908, i, 28.

[13] We must clearly differentiate, of course, between the so-called neighborhood or pressure symptoms of infundibular tumors and the nutritional disturbances which are due to the direct implication of the pituitary body itself.

It is hoped that the experiments which have been briefly recounted will serve in a measure to clear away some of these obscurities, or at least establish a basis for further investigation. Doubtless an overactive gland may present but slight enlargement, or at least may show no definite tumor growth, just as hyperthyroidism need not necessarily be accompanied by any great increase in size of the thyroid gland. Certain surgical experiences in cases of akromegaly, notably a case of Hochenegg's, reported by Stumme, and a case of my own, with a measurable subsidence of the manifestations of overgrowth, suggest that this disease is actually due to overactivity of the pars anterior of the gland; and if Schäfer's recent feeding experiments are to be confirmed, they add further support to this view.

The persistence of the characteristics of infantilism in a number of our puppies subjected to a partial hypophysectomy, and the occasional evidence of secondary atrophy of the sexual organs, together with the appearance of adiposity in several of the adult animals, suggests that the cases in which an hypophyseal tumor has been found in common with symptoms of adiposity and either a persistence of sexual infantilism or a secondary sexual degeneration, point toward the lowering of hypophyseal activity as the explanation of this clinical syndrome.

Doubtless there are many border-line cases in which the symptoms are less outspoken, as is true of moderate grades of over- or under-activity of the thyroid; and it is quite probable too that some of the confusing cases of gigantism, or akromegaly, which become impotent or have amenorrhœa with more or less marked adiposity are cases in which a gland with primary functional hypertrophy has become transformed into the well-recognized malignant adenoma,[14] leading in the course of time to interruption of normal secretion with the production of symptoms which we recognize as being due to a lessening of the functional activity of the gland. In similar fashion myxœdema may replace hyperthyroidism. We have recently observed a patient with an hypophyseal tumor in whom a beginning adiposity with impotence indicated an existing state of hypopituitarism; but an *x*-ray of the hands showed unmistakable evidence of an unsuspected akromegalic change in the bones, presumably a relic of an earlier stage of the glandular disease which was accompanied by oversecretion.

This will, of course, be recognized as merely a rough working hypothesis which leaves many things unexplained, for considering these various phenomena as due to alterations of the pars anterior, it leaves the function of the posterior lobe largely out of consideration.

The epithelial investment of this lobe (*pars intermedia:* Herring) is doubtless an important part of the gland, the function of which is not fully established, though the hemodynamic and other properties contained in extracts of this lobe are doubtless due to the secretory activity of these cells. Herring first called attention to the fact that their secretion in the form of hyaline globules, observable under the microscope, passes into the abundantly canalized tissue of the pars nervosa and could be traced upward until it emerged between the ependymal cells, to pass directly into the infundibular cavity of the ventricle. Our sections fully corroborate this observation of Herring's, and under certain conditions of experimentation we have seen the secretion greatly augmented in amount.[15]

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[14] Löwenstein. Virchow's Archiv. 1907, clxxxviii.

With full acceptance of this view, therefore, it is but natural that conditions which cause a stasis of cerebrospinal fluid, such as hydrocephalus, whether of the primary or acquired type, will lead to a damming back of the secretion. This we have found to be the case. The pars nervosa is often overfilled with the hyaline globules, which may even be seen in certain sections in the infundibular cavity. Large retention cysts of colloid are often observed under these circumstances, but this material is basophilic and, so far as we have been able to tell from injections, it does not contain the active principle of the posterior lobe. It is not improbable that the hyaline globules which take an acid stain are chemically modified by their passage through the pars nervosa.

In almost all cases of brain tumor, whether associated with hydrocephalus or not, we have found morphological as well as histological evidences not only of this retention of posterior lobe secretion, but of pressure on the gland as a whole. This glandular deformation may be considerable, and varies from a slight cup-shaped depression to a scaphoid configuration of the gland, which may be compressed until it measures only two or three millimeters in thickness, with marked histological alteration in the cells, particularly those of the anterior lobe. It is not unusual for patients with either primary hydrocephalus or brain tumors to show a tendency to become adipose despite the serious nature of their underlying malady. It is well known also that amenorrhœa and impotence are common disturbances in tumor cases, and it is not improbable that these symptoms may be secondary to hypophyseal insufficiency such as we have described. This view has been advanced by Marienesco and others for conditions of hydrocephalus.[16]

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[15] We have recently had the opportunity of studying the tissues from an excessively obese individual who died from the pressure effects of a large adenomatous tumor at the base of the brain. Dr. Crowe was fortunate enough, in studying a section through this growth, to discover a normal, though compressed, hypophyseal anterior lobe with undoubted evidence that the growth originated from the pars intermedia alone. The tumor resembled in its arrangement of acini containing colloid one which might have originated from the thyroid gland itself. The view has been advanced that the hypophysis may act vicariously for the thyroid, though there seems to be no justifiable grounds for this belief, as their extracts give quite contrary results, and the hypophysis, as has been stated, is iodine-free.

[16] Marienesco and Goldstein, Revue neurologique, 1909, xvii, 1000.

Before one can hope to interpret the pathological alterations of the hypophysis in disease, information is necessary in regard to its cellular appearance in different states of normal physiological activity, and this as yet has not been thoroughly acquired. There are three varieties of cells distinguishable by their variable staining reactions. The coarsely granular acidophile cells of the normal (resting ?) gland tend to lie in rows along the vascular sinuses. There occur also, in smaller numbers, large basophilic cells, while the centre of the columns or acini is filled with cells of an indifferent staining reaction—the *Hauptzellen* of the Germans. It is to be noted that the anterior lobe cells, as well as those of the pars intermedia under certain conditions (normal or pathological?), may secrete colloid, and this or a hyaline-like substance may even be seen within the blood sinuses of the gland; nevertheless, we must regard the cells of the pars anterior and the pars intermedia as differing widely in function, and there may, indeed, be more than one active principle in each division of the gland.

The coarsely granular acidophile elements were thought by Benda[17] to represent the active stage of the anterior lobe cells, a view supported later by Dean Lewis, who has made a most careful study of the histological appearances in a case of akromegaly unaccompanied by tumor. During the course of our experiments we have attempted to determine the histological characteristics of the glandular hypertrophy which would be presumed to occur in cases of survival after a partial removal of the anterior lobe, and it is our impression, from the study of these sections and from certain experiments made by Dr. Crowe upon the effect of pylocarpine administration in animals presumed to retain an active fragment of gland, that the large vesicular type of cell, largely free from granules, represents the active, or at least the discharged stage; the abundantly filled chromophile cells, on the other hand, representing a resting or storage stage which does not necessarily indicate great functional activity.

It is quite possible that Scaffidi[18] is correct in his view that the various anterior lobe cells do not represent stages of activity of one and the same cell, but that they actually have different properties. Erdheim and Stumme's recent studies of the histological alterations of the gland in pregnancy[19] might also be regarded as an argument favoring this conception, for in this condition it is the central cells (*Hauptzellen*) which appear to become active and to fill the cell columns at the expense of and with the relative disappearance of the chromophile elements, which remain few in number and instead of lining the sinuses are crowded to the centre of the columns. The distribution of these cells, as Dr. Goetsch has shown, is well brought out by the use of iron-hematoxylin stains, which pick out the chromophile granules in unmistakable fashion. We have had an opportunity of confirming these findings of Erdheim and Stumme's, and similar careful studies of a series of glands in other physiological states will doubtless show corresponding clean-cut alterations from the supposedly normal in the histological picture.

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[17] Berliner klin. Wochenschr., 1900, xxxvii, 1205.

[18] Archiv f. microscop. Anat., 1904, lxiv, 235.

[19] Beiträge z. path. Anat. u. z. allg. Path., 1909, xlvi, 1.

The weight of the hypophysis is somewhat greater in the female than the male, being slightly over 0.5 gram in the former and slightly under this weight in the latter. There is, however, a marked increase in the weight of the gravid gland, the particular specimen which we have had an opportunity of studying weighing 0.85 gram at the termination of pregnancy. The glands, on the other hand, from cases of intracranial tumor have been quite uniformly underweight.

Material taken at random from a series of indiscriminate autopsies has given us no special information of value. Through the kindness of Dr. Adolph Meyer we have had the opportunity of studying a series of 75 glands from the Worcester Hospital—a source similar to that from which Halliburton, Candler, and Sikes secured their material—and although histological alterations are present in the majority of them, it would be impossible to draw safe deductions without a thorough knowledge of the exact intracranial conditions and of correlating the findings with alterations in the ductless glands elsewhere from the same individual.

SUMMARY. It may be said that the pituitary body is a double organ in the sense that the secretion of its anterior and solidly epithelial portion discharges into the blood sinuses which traverse this part of the gland; whereas the hyaline substance, apparently the product of secretion from the epithelial investment of the posterior lobe, enters the cerebrospinal space by way of channels in the pars nervosa. Though possessing a physiologically active principle. as shown by the results of injections, the secretion of the posterior lobe does not seem to be so vitally essential to physiological equilibrium as that of the anterior lobe, the total removal of which leads to death with a peculiar train of symptoms which set in at an early date in the adult and after a longer interval in younger animals.

Alterations in the gland, which often ultimately assume the character of a malignant growth (adenoma) but which presumably, at least in their earlier stages, represent an hypertrophy, are common in clinical conditions of overgrowth (akromegaly and gigantism), and certain feeding experiments lend support to the view that these clinical states represent the consequences of hyperactivity of the pars anterior. Partial removals of the anterior lobe usually lead to obvious disturbances of metabolism accompanied oftentimes by adiposity and in the young by a persistence of infantilism, or in adults by a tendency to lose the secondary sexual characteristics already acquired. These experimental conditions are comparable to those which have been recognized clinically as accompaniments likewise of tumors in the hypophyseal region, which under these circumstances can therefore be interpreted as lesions which through pressure have led to lessened glandular activity.

In view of the apparent interrelation of many of the glands of internal secretion it is quite probable that certain of the symptoms known to accompany hypophyseal disease may be consequent upon a secondary change in other glands which follows the primary lesion of the hypophysis. These changes are seemingly more outspoken and more widespread after a lesion of the pituitary body than after a corresponding lesion of any other individual member of the group of ductless glands, and in view of its unusually well-protected position one might have conjectured that it must represent a vitally important organ.

AN ACUTE INFECTIOUS DISEASE OF UNKNOWN ORIGIN.

A CLINICAL STUDY BASED ON 221 CASES.

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For many years great confusion prevailed about the two diseases which are now known as typhus and typhoid fever, even after clinical knowledge of these diseases had separated them from the large group of "pestilential fevers" with which they had previously been confounded. This confusion was due to the fact that, irrespective of the lack of pathological investigation and the ignorance of the causative factors of these diseases, no well systematized analysis of the clinical features of them had been carried on. At the end of the eighteenth and the beginning of the ninteenth centuries the first great work on the differentiation of typhus and typhoid fevers was begun. We owe to Prost,[1] in France, the recognition of the intestinal lesions as the important distinctive lesion of typhoid fever. Even with the great contribution of Petit and Serres,[2] who followed and elaborated on Prost's work, showing that the lesion was limited especially to the lower part of the small intestine, and of Bretonneau,[3] of Tours, that the

[1] Médecine éclairée par l'observation et l'ouverture des corps, Paris, 1804.

[2] Traité de la Fièvre Entéro-mésentérique, Paris, 1813.

[3] De la maladie, à laquelle M. Bretonneau a donné le nom de dothiénentérie, ou de dothiénertérite, Arch. gén. de méd., 1826, ser. 1, tom. x, 169. Notice sur la contagion de la dothiénentérité. Arch. gén. de méd., ser. 1, xxi; also, de la dothiénentérité, Arch. gén. de méd., 1826.